

REMARKS

It is the Examiner's position that the instant restriction is primarily a mechanism for seeking clarification and preferably amendment of the claims because the variable X_{aa_0} is undefined and can only be defined by introducing new matter. It is also the Examiner's position that it cannot be determined if the claimed inventions are or are not distinct.

Accordingly, claim 1 has been amended to recite the compound of formula (I) which finds support on page 2, line 29 of the specification.

It is also the Examiner's position that there are typographical errors in the claims and that correction will be required.

Applicants respectfully submit that they would be pleased to correct any typographical errors which the Examiner identifies.

CONCLUSION


Entry of this amendment and allowance of claims 1-39 is respectfully requested.



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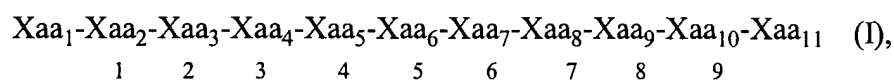
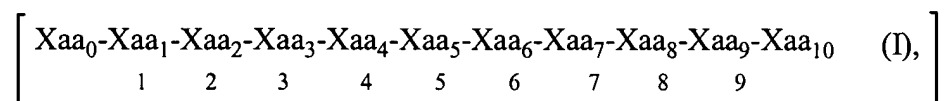

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Appendix A

VERSION OF CLAIM WITH MARKINGS TO SHOW CHANGES MADE

Patent Application Ser. No. 09/703,233

1. (Amended). A compound having a formula:



or a pharmaceutically acceptable salt thereof, wherein

at least one amide bond of an amino acid residue represented by Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, and Xaa₁₀ is N-alkylated;

Xaa₁ is absent or Xaa₁ is selected from the group consisting of hydrogen, N-methylprolyl, and an acyl group, wherein the acyl group is selected from the group consisting of

R¹-(CH₂)_n-C(O)-, wherein n is an integer from 0 to 8 and R¹ is selected from the group consisting of N-acetylamino, alkoxy, alkyl, aryl, carboxy, cycloalkenyl, cycloalkyl, heterocycle, and hydroxy; and

R²-CH₂CH₂-O-(CH₂CH₂O)_p-CH₂-C(O)-, wherein p is an integer from 1 to 8 and R² is selected from the group consisting of hydrogen, N-acetylamino, and alkyl;

provided that Xaa₁ is absent only when Xaa₂ is N-(R³)-prolyl;

Xaa₂ is an N-alkylated amino acid selected from the group consisting of N-(R³)-alanyl, N-(R³)-glycyl, N-(R³)-norvalyl, and N-(R³)-prolyl, wherein R³ is C₁-C₅-alkyl; or Xaa₂ is an N-unalkylated amino acid selected from the group consisting of

β-alanyl,

D-alanyl,

4-aminobutyryl,

(1R,3S)-1-aminocyclopentane-3-carbonyl,
(1S,3R)-1-aminocyclopentane-3-carbonyl,
(1R,4S)-1-aminocyclopent-2-ene-4-carbonyl,
(1S,4R)-1-aminocyclopent-2-ene-4-carbonyl,
asparaginyll,
3-(4-chlorophenyl)alanyl,
3-(4-cyanophenyl)alanyl,
glutaminyl,
glutamyl,
glycyl,
4-hydroxyprolyl,
3-(4-methylphenyl)alanyl,
prolyl,
seryl, and
threonyl;

Xaa₃ is an N-alkylated amino acid selected from the group consisting of N-(R³)-alanyl, N-(R³)-glycyl, N-(R³)-leucyl, and N-(R³)-phenylalanyl, wherein R³ is as defined above; or Xaa₃ is an N-unalkylated amino acid selected from the group consisting of

alanyl,
(1S,3R)-1-aminocyclopentane-3-carbonyl,
(1S,4R)-1-aminocyclopent-2-ene-4-carbonyl,
asparaginyll,
aspartyl,
3-(3-cyanophenyl)alanyl,
3-(4-cyanophenyl)alanyl,
glutaminyl,
glycyl,
leucyl,
lysyl(N-epsilon-acetyl),
3-(4-methylphenyl)alanyl,
norvalyl,
prolyl, and
phenylalanyl;

Xaa₄ is an N-alkylated amino acid selected from the group consisting of N-(R³)-alanyl, N-(R³)-glycyl, N-(R³)-homophenylalanyl, N-(R³)-isoleucyl, N-(R³)-leucyl, N-(R³)-norvalyl, N-(R³)-phenylalanyl, N-(R³)-D-phenylalanyl, N-(R³)-seryl, N-(R³)-tyrosyl, N-(R³)-valyl, and N-(R³)-D-valyl, wherein R³ is as defined above; or

Xaa₄ is an N-unalkylated amino acid selected from the group consisting of

- alanyl,
- alloisoleucyl,
- allylglycyl,
- 2-aminobutyryl,
- (1R,4S)-aminocyclopent-2-ene-4-carbonyl,
- asparaginylyl,
- aspartyl,
- 3-[2-(5-bromothiophenyl)]alanyl,
- 3-(3-chlorophenyl)alanyl,
- 3-(4-chlorophenyl)alanyl,
- 3-(3-cyanophenyl)alanyl,
- cyclohexylalanyl,
- 3-(3,4-dimethoxyphenyl)alanyl,
- 3-(3-fluorophenyl)alanyl,
- 3-(4-fluorophenyl)alanyl,
- glutaminyl,
- glycyl,
- histidyl,
- homophenylalanyl,
- homoseryl,
- isoleucyl,
- leucyl,
- lysyl(N-epsilon-acetyl),
- methionyl,
- methionyl(sulfone),
- 3-(4-methylphenyl)alanyl,
- 3-(naphth-1-yl)alanyl,
- 3-(naphth-2-yl)alanyl,
- norornithyl,
- norvalyl,
- phenylalanyl,

phenylglycyl,
prolyl,
3-(3-pyridyl)alanyl,
3-(4-thiazolyl)alanyl,
3-(2-thienyl)alanyl,
seryl,
seryl(O-benzyl),
styrylalanyl,
tryptyl,
tyrosyl,
valyl, and
D-valyl;

Xaa₅ is an N-alkylated amino acid selected from the group consisting of N-(R³)-D-homophenylalanyl, N-(R³)-D-isoleucyl, N-(R³)-D-leucyl, and N-(R³)-D-phenylalanyl, wherein R³ is as defined above; or Xaa₅ is an N-unalkylated amino acid selected from the group consisting of

D-alanyl,
alloisoleucyl,
D-alloisoleucyl,
D-2-aminobutyryl,
D-3-(4-aminophenyl)alanyl,
D-asparaginyll,
D-3-(3-benzothiienyl)alanyl,
D-*t*-butylglycyl,
D-(chlorophenyl)alanyl,
D-citrullyl,
D-3-(3-cyanophenyl)alanyl,
D-cyclohexylalanyl,
cyclohexylglycyl,
D-cysteinyl(S-acetamidomethyl),
D-cysteinyl(S-*t*-butyl),
D-3-(3,4-difluorophenyl)alanyl,
D-(3,4-dimethoxyphenyl)alanyl,
D-glutaminyll,
glycyl,

D-homophenylalanyl,
D-homoseryl,
isoleucyl,
D-isoleucyl,
D-leucyl,
D-lysyl(N-epsilon-nicotinyl),
D-lysyl,
D-methionyl,
D-3-(4-methylphenyl)alanyl,
D-3-(naphth-1-yl)alanyl,
D-3-(naphth-2-yl)alanyl,
D-3-(4-nitrophenyl)alanyl,
D-norleucyl,
D-ornithyl,
D-penicillaminyl(S-acetamidomethyl),
D-penicillaminyl(S-benzyl),
D-penicillaminyl(S-methyl),
D-penicillaminyl,
D-3-(pentafluorophenyl)alanyl,
D-phenylalanyl,
D-prolyl,
D-seryl(O-benzyl),
D-seryl,
D-(2-thienyl)alanyl,
D-threonyl(O-benzyl),
D-threonyl,
D-3-(3-trifluoromethylphenyl)alanyl,
D-(3,4,5-trifluorophenyl)alanyl,
D-tryptyl,
D-tyrosyl(O-ethyl),
D-tyrosyl, and
D-valyl;

Xaa₆ is an N-alkylated amino acid selected from the group consisting of N-(R³)-aspartyl, N-(R³)-glutamyl, N-(R³)-glycyl, N-(R³)-seryl, N-(R³)-threonyl, N-(R³)-threonyl(O-benzyl), and N-(R³)-tyrosyl, wherein R³ is as defined above; or Xaa₆ is

an N-unalkylated amino acid selected from the group consisting of

alanyl,
allothreonyl,
D-allothreonyl,
allylglycyl,
asparaginyll,
aspartyl,
glutaminyll,
glycyl,
histidyl,
homoseryl,
D-homoseryl,
3-(4-hydroxymethylphenyl)alanyl,
isoleucyl,
lysyl(N-epsilon-acetyl),
methionyl,
3-(naphth-2-yl)alanyl,
norvalyl,
octylglycyl,
prolyl,
3-(3-pyridyl)alanyl,
seryl,
D-seryl,
threonyl,
D-threonyl,
tryptyl,
tyrosyl, and
tyrosyl(O-methyl);

Xaa₇ is an N-alkylated amino acid selected from the group consisting of N-(R³)-alanyl, N-(R³)-glycyl, N-(R³)-isoleucyl, N-(R³)-leucyl, N-(R³)-D-leucyl, N-(R³)-norleucyl, N-(R³)-norvalyl, N-(R³)-seryl, N-(R³)-threonyl, and N-(R³)-valyl, wherein R³ is as defined above; or Xaa₇ is an N-unalkylated amino acid selected from the group consisting of

alanyl,
allothreonyl,

allylglycyl,
3-(4-amidophenyl)alanyl,
2-aminobutyryl,
arginyl,
asparaginyll,
cyclohexylalanyl,
glutaminyll,
D-glutaminyll,
glycyl,
homoalanyl,
homoseryl,
4-hydroxypropyl,
leucyl,
D-leucyl,
lysyl(N-epsilon-acetyl),
methionyl sulfone,
methionyl sulfoxide,
methionyl,
norleucyl,
norvalyl,
D-norvalyl,
octylglycyl,
ornithyl(N-delta-acetyl),
phenylalanyl,
propargylglycyl,
seryl,
D-seryl,
threonyll,
tryptyl,
tyrosyl, and
valyl;

Xaa₈ is an N-alkylated amino acid selected from the group consisting of N-(R³)-alanyl, N-(R³)-D-alanyl, N-(R³)-isoleucyl, and N-(R³)-leucyl, wherein R³ is as defined above; or Xaa₈ is an N-unalkylated amino acid selected from the group consisting of

alanyl,
alloisoleucyl,
D-alloisoleucyl,
allylglycyl,
citrullyl,
glycyl,
isoleucyl,
D-isoleucyl,
leucyl,
D-leucyl,
lysyl(N-epsilon-acetyl),
D-lysyl(N-epsilon-acetyl),
methionyl,
3-(naphth-1-yl)alanyl,
norvalyl,
prolyl,
D-prolyl, and
valyl;

Xaa₉ is the N-alkylated amino acid N-(R³)-arginyl, wherein R³ is as defined above;
or Xaa₉ is an N-unalkylated amino acid selected from the group consisting of

[(4-amino-N-isopropyl)cyclohexyl]alanyl,
3-(4-amino-N-isopropylphenyl)alanyl,
arginyl(N^GN^{G'} diethyl),
arginyl,
D-arginyl,
citrullyl,
glutaminyl,
3-(4-guanidinophenyl)alanyl,
histidyl,
homoarginyl,
lysyl(N-epsilon-isopropyl),
lysyl(N-epsilon-nicotinyl),
lysyl,
norarginyl,
ornithyl,

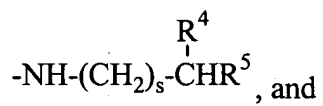
ornithyl[N-delta-(2-imidazolyl)],
ornithyl(N-delta-isopropyl), and
3-(3-pyridyl)alanyl;

Xaa₁₀ is an N-alkylated amino acid selected from the group consisting of N-(R³)-alanyl, N-(R³)-D-alanyl, N-(R³)-glycyl, N-(R³)-homoalanyl, and N-(R³)-norvalyl, wherein R³ is as defined above; or Xaa₁₀ is an N-unalkylated amino acid selected from the group consisting of

D-alanyl,
2-aminobutyryl,
D-2-aminobutyryl,
2-aminoisobutyryl,
3,4-dehydroprolyl,
4-hydroxyprolyl,
phenylalanyl,
prolyl,
D-prolyl,
1,2,3,4-tetrahydroisoquinoline-3-carbonyl, and
D-valyl; and

Xaa₁₁ is a hydroxy group or an amino acid amide selected from the group consisting of:

alanylamide,
D-alanylamide,
alanylethylamide,
D-alanylethylamide,
azaglycylamide,
glycylamide,
glycylethylamide,
lysyl(N-epsilon-acetyl),
D-lysyl(N-epsilon-acetyl),
N-methyl-D-alanylamide,
sarcosylamide,
serylamide,
D-serylamide,
a residue represented by the formula



a group represented by the formula $-\text{NH}-\text{R}^6$; wherein

s is an integer from 0 to 8;

R^4 is selected from the group consisting of hydrogen, alkyl, and a 5- to 6-membered cycloalkyl ring;

R^5 is selected from the group consisting of hydrogen, alkoxy, alkyl, aryl, cycloalkenyl, cycloalkyl, heterocycle, and hydroxy;

provided that s is not zero when R^5 is hydroxy or alkoxy; and

R^6 is selected from hydrogen and hydroxy.